Pergamon

Tetrahedron Letters 41 (2000) 6285–6288

TETRAHEDRON LETTERS

A convenient method for the preparation of hydroxamic acids

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Received 11 April 2000; revised 12 June 2000; accepted 13 June 2000

Abstract

A one-step conversion of carboxylic acid to hydroxamic acid, under neutral pH conditions is described. This simple, selective and efficient method was applied to a wide range of aliphatic/aromatic carboxylic acid derivatives that contain hydroxyl, halo, ester and other base sensitive groups as substituents. The method utilizes cheaply available reagents and hence it is a practical and cost effective strategy, compared to the other methods available in the literature.

Keywords: hydroxamic acid; metalloenzymes; carboxylic acid and antibiotics.

Hydroxamic acid derivatives possess a wide spectrum of biological activities such as anti-inflammatory, antiasthmatic, antimetastatic, antibiotic, psychotropic, insecticidal, acaricidal and nematocidal activity.[1a–e] They also inhibit various other enzymes such as metalloenzymes.[2] Several methods are available for the preparation of hydroxamic acids and have been well-documented in the literature.[3a–j] The common method for the preparation of these compounds is via the reaction of *O*/*N*-protected hydroxylamine such as NH_2-*O*-Bn, *N*-*t*-BOC-*O*-THP, *N*-*t*-BOC-*O*-TBDMS, *N*,*O*-bis(phenoxycarbonyl)hydroxylamine, *N*,*O*-bis(tert-butoxycarbonyl)hydroxylamine and *N*,*N*,*O*-tris(trimethylsilyl)hydroxylamine with activated carboxylic acids.[4a–d] However, these methods utilize highly expensive hydroxylamine reagents and some of them are not commercially available. The economical way of making hydroxamic acid derivative is the reaction of hydroxylamine with acid chlorides or esters.[5]

Preparation of acid chlorides is often tedious when other acid labile functional groups present in the substrate. Also, it will be very difficult to prevent further acylation during the reaction with hydroxylamine. In our experience, reaction of hydroxylamine with esters does not proceed under

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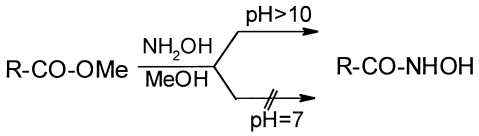
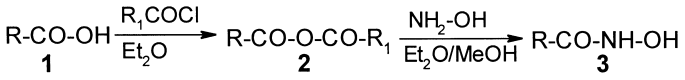
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01058-3

neutral conditions (Scheme 1); it always needs an alkaline condition (pH > 10). Hence, this method is not suitable if one needs to perform this reaction on ester derivatives that contain halides, esters and other base-sensitive groups.



Scheme 1.

As a part of our drug discovery program we needed to make the hydroxamic acid derivatives from the corresponding carboxylic acid derivatives. None of the literature methods mentioned above gave the required product in good yield when using hydroxylamine. Therefore, we have developed a mild and simple one-step approach for the preparation of hydroxamic acids from carboxylic acid derivatives as shown in Scheme 2.



Scheme 2.

A typical experimental procedure is as follows: To a solution of the isobutyric acid (0.88 g, 10 mmol) in diethylether (30 mL) at 0°C ethylchloroformate (1.3 g, 12 mmol) and *N*-methylmorpholine (1.3 g, 13 mmol) were added and the mixture was stirred for 10 min. The solid was filtered off and the filtrate was added to freshly prepared hydroxylamine (0.5 g, 15 mmol) in methanol.[6] The reaction mixture was stirred at room temperature for 15 min. The solvent was evaporated and the residue was purified by silica gel column chromatography to obtain the isobutyrohydroxamic acid (0.83 g, 81%).

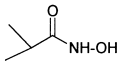
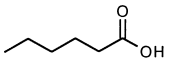
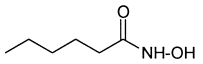
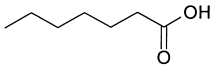
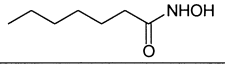
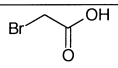
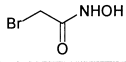
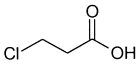
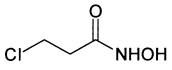
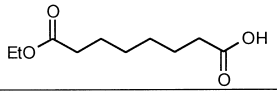
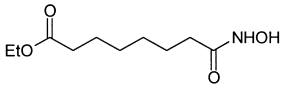
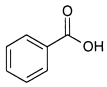
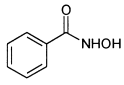
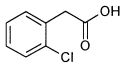
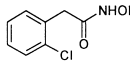
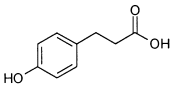
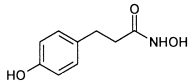
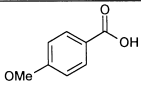
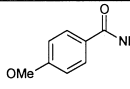
Further, the method was successfully extended to the synthesis of a variety of hydroxamic acid derivatives from the carboxylic acids under neutral conditions. In all cases, the yields were higher than 80% (Table 1). In addition, by-products such as *N*, *O* and triacylated derivatives that are usually formed in the reaction of acid chlorides with hydroxylamine were not observed in this case. Hence, this method is simple, selective and works equally well with aliphatic/aromatic carboxylic acid derivatives that contain hydroxyl, halo and ester groups as additional substituents.

In order to establish the reaction pathway, the reaction of methylhexanoate with hydroxylamine in methanol (pH = 7) was performed at room temperature for 24 h. Surprisingly, no trace of the corresponding hydroxamic acid was found and the whole starting material was recovered. Based on the above result the formation of methylester intermediate was ruled out and the formation of the hydroxamic acid derivative could proceed via anhydride **2** (Scheme 2).

This method is simple and convenient as it does not require any crucial work-up of the reaction that involves acidification with resins[5] or making a copper complex and liberation with H_2S.[7] We also found that this method works equally well with triethylamine in the place of *N*-methylmorpholine.

In conclusion, we report a mild and efficient method for the preparation of hydroxamic acid derivatives under neutral pH conditions, that is suitable for a variety of substituted carboxylic

Table 1
Preparation of hydroxamic acids from hydroxylamine and carboxylic acids

S. No	Carboxylic acid (1)	Reaction time (min)	Product (2)	m.p. (Lit. m.p) (^{o}C)	Yield* (%)
1		15		118-120 (116)[4d]	81
2		15		63-65 (65)[4d]	95
3		15		73-75 (75-76)[4d]	91
4		10		95-98	82
5		15		90-92	80
6		15		60-62	92
7		30		123-124	94
8		30		152-153	85
9		30		143-145	81
10		90		169-171	86

*All compounds were purified by column chromatography and gave satisfactory ^{1}HNMR, MS and elemental analysis.

acids. Application of this methodology to the chiral carboxylic acids and synthesis of natural product is in progress.

Acknowledgements

The authors wish to thank Penn Bio-Organics, Inc. for financial support and encouragement.

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6. Hydroxylamine was prepared according to the procedure described by Devlin, J. P. et al. in Ref. 5: Hydroxylamine hydrochloride (1 g, 15 mmol) in methanol (10 mL) was added to a stirred solution of potassium hydroxide (0.84 g, 15 mmol) in methanol (4 mL) at 0°C. The mixture was stirred for 15 min at the same temperature and the precipitated potassium chloride was removed and the filtrate was used as such.
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